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13. ABSTRACT (Maximum 200 Words)

A history of benign breast disease is associated with an increase in risk of breast cancer, however the risk differs according to a number of important parameters. These may include age, histologic characteristics of the benign lesion, family history of breast cancer, and other factors. The purpose of this research was to investigate the relation between prior benign breast disease and subsequent breast cancer in a cohort of women who underwent mammography in a defined population at Group Health Cooperative, a large health maintenance organization in western Washington state. Women were eligible for study if they underwent mammography at GHC, reported a history of prior breast biopsy at least one year prior to their mammogram, and had no history of prior breast cancer. A total of 17,714 women met study criteria. Of these women, 521 were diagnosed with breast cancer subsequent to their benign biopsy and comprised the "case" group for the present study. These cases were matched to the pool of the remaining 17,193 women with prior breast biopsy and no subsequent breast cancer on the basis of date of mammogram at Group Health Cooperative using a 1:4 ratio, and compared on the basis of key characteristics.

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Introduction

A history of benign breast disease is associated with an approximate two-fold increase in risk of breast cancer, however risk differs according to the histological characteristics of BBD and other factors. Although histopathology identifies women with BBD with increased risk of breast cancer, such as women with atypical hyperplasia, few women with BBD fall into this high risk categories and most will not go on to develop breast cancer. In contrast, many women with "low risk" benign lesions are subsequently diagnosed with breast cancer and for these women, the histopathology of their BBD is not a useful predictor of risk. The purpose of this research was to improve understanding of the relation between BBD and subsequent breast cancer in a defined cohort of women with prior BBD. Using a nested case-control design, this project examined the relation between histologic type of BBD and other established risk factors with risk of breast cancer.

Body

The approved statement of work consisted of four study aims. Each aim is listed below, accompanied by the accomplishments associated with that aim.

Aim 1: To assemble a cohort of approximately 4500 women who underwent excisional breast biopsy between 1994 and 2002, this event is termed the index biopsy.

To meet this aim, we quickly determined that we could not easily distinguish between excisional breast biopsy and other methods for histology/cytology for eligibility purposes. Nor could we easily determine the timing of the prior biopsy. Thus, we first identified 21,176 women who had undergone any prior breast biopsy and had a mammogram during the study period.

Aim 2: To identify approximately 210 women who subsequently developed breast cancer at least one year following their benign biopsy.

From the 21,176 women with prior biopsy identified in Aim 1 (above), 521 were subsequently diagnosed with breast cancer, 424 of these women were diagnosed with invasive disease. A major problem encountered in completing this task was related to the biopsy procedure. We originally proposed identifying cases (and controls) who underwent excisional breast biopsy, so that sufficient material would be available for future studies. Through the course of the present study, we quickly learned that biopsy procedure was not uniformly available. Thus we initially ascertained cases on the basis of any prior benign breast biopsy. Descriptive

characteristics of these cases are given in Table 1.

Table 1: Descriptive characteristics of breast cancer cases with prior benign breast biopsy (n=521)[1]

	n	%
Age at diagnosis		
<50	55	10.6
50-59	140	26.9
60-69	130	25.0
70+	196	37.6
Race		
White	482	92.5
African American	11	2.1
Asian	22	4.2
Other	6	1.2
Stage at diagnosis		
in situ[2]	97	18.7
localized	324	62.4
regional	94	18.1
distant	4	0.8
Interval (yrs) since prior benign biopsy and cancer diagnosis		
1-4	50	12.3
5-9	103	25.3
10+	255	62.5

1. Women with missing information are excluded from column totals
2. SEER summary stage

Aim 3: To match breast cancer cases (identified in Aim 2) to at least 3 control women with similar benign breast pathology who remained cancer-free

We matched each breast cancer case to 4 control women, on the basis of age at diagnosis (cases) or mammogram (controls). Similar to cases, control women underwent benign breast biopsy at least one year prior to their subsequent mammogram (index exam). Thus, 2084 controls were available for analysis.

Descriptive characteristics of controls are given in Table 2.

Table 2: Descriptive characteristics of control women with prior benign breast biopsy (n=2084)[1]

	n	%
Age at mammogram (index exam)		
<50	600	28.8
50-59	602	28.9
60-69	424	20.4
70+	458	21.9
Race		
White	1824	89.6
African American	77	3.8
Asian	95	4.7
Other	40	2.0
Interval (yrs) since prior benign biopsy and cancer diagnosis		
1-4	519	31.3
5-9	286	17.2
10+	854	51.5

1. Women with missing information are excluded from column totals

Similar to Task 2 (above) we encountered difficulty in ascertaining method of excisional biopsy for a majority of study women. A long-term aim of this project was to identify benign breast tissue that could be studied in future research in order to identify potential molecular markers of risk in women with BBD. As shown below (Aim 4) we conducted sub-analysis on the subset of cases and control for whom slides and fixed specimens are available.

Aim 4: To compare cases and controls on the basis of epidemiologic risk factors for breast cancer and retrieve slides and paraffin-embedded tissue from the benign biopsy event for future studies of molecular (genetic) markers of breast cancer risk.

To meet this aim, we abstracted risk information for breast cancer, including: age, race, family history, use of hormone replacement therapy, and mammographic breast density. Sub analysis was conducted to examine the risk of breast cancer associated with histologic result of the benign breast lesion among cases and controls with known pathologic findings. This analysis was limited to the 241 study women for whom retrievable tissue is available. The primary findings associated with aim are shown in Table 3.

Table 3. Risk of breast cancer among women with prior benign breast biopsy[1]

Characteristic	Cases	Controls	RR	95% CI
Age at index exam				
<50	104	600	1.00[2]	
50-59	143	602	1.30	1.03-1.64
60-69	120	425	1.49	1.18-1.89
70+	154	458	1.70	1.36-2.13
		P for trend <0.001		
First degree family history of breast cancer [3,4]				
No	383	1669	1.00[2]	
Yes	134	403	1.39	1.11-1.74
Menopausal status				
Pre- or peri-menopause	117	577	1.00[2]	
postmenopause	396	1490	1.22	0.88-1.68
Use of hormone replacement therapy				
No	183	932	1.00[2]	
Yes	330	1116	1.38	1.11-1.72
Mammographic breast density[3]				
Almost entirely fat/scattered fibroglandular tissue	164	819	1.00[2]	
Heterogeneously dense/extremely dense	320	1132	1.66	1.33-1.06
Prior benign biopsy result[3]				
Normal/benign	30	27	1.00[2]	
Other benign	30	60	0.88	0.45-1.72
Proliferative benign[5]	47	47	2.03	1.10-3.74

1. women with missing information excluded from column totals
2. baseline risk
3. Risk estimates adjusted for age
4. Breast cancer in a mother, daughter and/or sister
5. Includes atypical hyperplasia, ductal hyperplasia and fibroadenoma

We undertook additional analysis (Table 4) restricted to women

with invasive breast cancer to investigate whether the risk of invasive breast cancer associated with selected risk factors was higher than estimates observed in analysis that included in situ disease.

Table 4. Risk of invasive breast cancer among women with prior benign breast biopsy[1]

Characteristic	Cases	Controls	RR	95% CI
Age at index exam				
<50	77	600	1.00[2]	
50-59	113	602	1.39	1.11-1.82
60-69	98	424	1.65	1.25-2.17
70+	136	458	2.01	1.56-2.60
		P for trend <0.0001		
First degree family history of breast cancer[3,4]				
No	310	1669	1.00[2]	
Yes	110	403	1.39	1.08-1.77
Menopausal status				
Pre- or peri-menopause	332	1490	1.00[2]	
postmenopause	86	577	1.14	0.79-1.63
Use of hormone replacement therapy				
No	142	932	1.00[2]	
Yes	274	1116	1.46	1.15-1.85
Mammographic breast density[3]				
Almost entirely fat/scattered fibroglandular tissue	136	819	1.00[2]	
Heterogeneously dense/extremely dense	258	1132	1.67	1.32-2.11
Prior benign biopsy result[3]				
Normal/benign	26	27	1.00[2]	
Other benign	22	60	0.77	0.38-1.58
Proliferative benign[5]	36	47	2.12	1.08-4.14

1. women with missing information excluded from column totals
2. baseline risk
3. Risk estimates adjusted for age
4. Breast cancer in a mother, daughter and/or sister
5. Includes atypical hyperplasia, ductal hyperplasia and fibroadenoma

A key limitation of the above analysis was the necessary reliance of the initial, clinical pathology report for the prior benign

lesions. In the absence of a standardized study review, it is expected that the potential for misclassification among these benign lesions is high. For this reason, the above analysis was deliberately crude, and grouped hyperplasias and fibroadenoma together as "proliferative benign" lesions. Future studies will not rely on the original pathologic interpretation and will instead include rigourous and expert pathologic review.

Key Research Accomplishments

- Identification of retrievable pathology for future studies

Reportable Outcomes

Mandelson MT, White E, Porter P. Selection bias when biopsied controls are used in biomarker research. Abstract. AACR October Meeting 2003.

Mandelson MT, White E, Porter P. Selection bias when biopsied controls are used in biomarker research. In preparation for submission to *Cancer Epidemiology , Biomarkers, and Prevention*

Mandelson MT, Porter P, Taplin, SH, White E. Benign breast disease: risk factors and mammographic features. In preparation for submission to *American Journal of Epidemiology*

Molecular alterations in benign breast tissue and risk of breast cancer in preparation for submission to NCI as RO1 Feb 1, 2005 (Peggy Porter, M.D. PI)

Conclusions

From the start, this project posed many significant challenges. Nevertheless, the key accomplishment of this study is the identification of a critical cohort of women with benign breast disease for future, molecular studies. There are few such resources available. As litigation in medicine increases, there is a disinclination for pathologic laboratories to retain fixed material beyond what is minimally required.